CLINICAL SCIENCE

Impact of glycemic control on the incidence of acute kidney injury in critically ill patients: a comparison of two strategies using the RIFLE criteria

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OBJECTIVE: To compare the renal outcome in patients submitted to two different regimens of glycemic control, using the RIFLE criteria to define acute kidney injury.

INTRODUCTION: The impact of intensive insulin therapy on renal function outcome is controversial. The lack of a criterion for AKI definition may play a role on that.

METHODS: Included as the subjects were 228 randomly selected, critically ill patients engaged in intensive insulin therapy or in a carbohydrate-restrictive strategy. Renal outcome was evaluated through the comparison of the last RIFLE score obtained during the ICU stay and the RIFLE score at admission; the outcome was classified as favorable, stable or unfavorable.

RESULTS: The two groups were comparable regarding demographic data. AKI developed in 52% of the patients and was associated with a higher mortality (39.4%) compared with those who did not have AKI (8.2%) ($p<0.001$). Renal function outcome was comparable between the two groups ($p=0.37$). We observed a significant correlation between blood glucose levels and the incidence of acute kidney injury ($p=0.007$). In the multivariate logistic regression analysis, only APACHE III scores higher than 60 were identified as an independent risk factor for unfavorable renal outcome. APACHE III scores>60, acute kidney injury and hypoglycemia were risk factors for mortality.

CONCLUSION: Intensive insulin therapy and a carbohydrate-restrictive strategy were comparable regarding the incidence of acute kidney injury evaluated using RIFLE criteria.

KEYWORDS: Critical illness; Insulin; Hypoglycemia; Renal failure; Glycemic control.

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INTRODUCTION

The Van de Berghe et al.[1] study (2001) introduced the concept of strict glycemic control for the critically ill patient, demanding a new approach in the treatment of hyperglycemia in the intensive care unit (ICU). This study demonstrated that treatment of patients admitted to a surgical ICU with a regimen of intensive insulin therapy (IIT) resulted in lower morbidity and mortality compared with those treated with standard glycemic control. The effect was particularly significant with regard to renal outcome; patients managed with IIT had a lower incidence of acute renal failure (defined as the need for renal replacement therapy [RRT]).

In a subsequent study performed in a medical ICU, Van den Berghe et al.[2] observed that the group treated with IIT had a lower incidence of newly-acquired acute kidney injury (AKI), as defined by increases in serum creatinine levels.

On the other hand, the VISEP[3] study compared IIT with a standard glycemic control strategy and did not find that the use of IIT benefited the renal outcomes of 488 patients. Moreover, this study was interrupted due to high rates of hypoglycemia. A meta-analysis that evaluated the impact of strict glycemic control on the prognosis of critically ill patients[4] did not show a reduced need for RRT. As with the VISEP study, the meta-analysis showed a higher incidence of hypoglycemia in patients receiving strict glycemic control. The NICE-SUGAR Study[5] that randomized 6104 patients and compared IIT with a conventional glycemic control did not find significant differences in the incidence of acute renal failure defined as the need for RRT.

There has been a lack of consensus regarding the definition of AKI. Many criteria are used in defining AKI,

including the need for dialysis as well as changes in serum creatinine levels, blood ureic nitrogen (BUN) levels and urinary output. As a consequence, it is difficult to compare the results produced by these different methods. The publication of the RIFLE criteria in 2004[6] had the objective of standardizing the AKI definition and proposed three graded levels of injury: Risk (R), Injury (I), Failure (F), and two outcome stages: Loss (L) and End-stage Kidney Disease (E). The RIFLE criteria were validated in large trials, making them a promising prognostic predictor.[7–10]

Recently, we performed a prospective randomized trial comparing the safety and efficacy of IIT and a carbohydrate-restrictive strategy (CRS) in a mixed population of critically ill patients. We did not find a significant difference in the rates of incidence of AKI (defined as the need for dialysis) between the two groups.[11] The objective of the present study was to compare the renal function outcome in the same group of patients by using the RIFLE criteria to define AKI.

METHODS

A retrospective analysis of clinical and laboratory data of patients included in the original prospective trial was performed. This study included all adult, non-pregnant patients admitted from July 1, 2004 to December 31, 2006 to a 20-bed, multidisciplinary ICU in a general hospital and an 11-bed trauma center ICU who had registered at least two blood glucose levels above 150 mg/dL from three measurements obtained within the first 12 hours of ICU admission. After written informed consent was obtained, patients were randomized to one of the glycemic control strategies:

Group 1 (Intensive Insulin Therapy). Continuous intravenous insulin infusion was adjusted to maintain glycemic levels less than 150 mg/dL; in stable patients levels were maintained between 80 and 120 mg/dL. Capillary glycemic measurements were obtained from the patients every two hours. The insulin dose was adjusted according to an algorithm run by nurses and overseen by physicians. These patients received glucosaline (5% glucose + 0.9 NaCl) hydration and enteral nutrition with a formula containing 45% carbohydrates, 17% proteins and 38% lipids (Diason, Nutricia Clinical Care Ltd).

Group 2 (Carbohydrate-Restrictive Strategy). Patients received intravenous hydration with a glucose-free solution (Ringer III) and enteral nutritional formula containing 33.3% carbohydrates, 16.7% proteins and 50% lipids (Glucerna, Abbott Laboratories). These patients received regular insulin subcutaneously according to a sliding scale with the goal of maintaining blood glucose levels less than 180 mg/dL; in stable patients, the goal was a level less than 150 mg/dL.

Hypoglycemia was defined as a blood glucose level of 40 mg or less per deciliter.

All patients had their basal creatinine level estimated by the Modification of Diet in Renal Disease (MDRD)[12] equation (glomerular filtration rate [GFR] $=186 \times [\text{serum creatinine}]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ woman}] \times [1.210 \text{ if North American black}]$), considering an acceptable GFR of 75 ml/min as suggested by the Acute Dialysis Quality Group (ADQI) in the publication of the RIFLE criteria. We did not use the variable of race because we were dealing with a mixed-race population; we also did not include any subjects self-identifying as North-American black. The equation with this modification had already been validated for a Brazilian population.[13]

The RIFLE category was determined based only on the GFR estimated by serum creatinine levels. Urinary output was not used because available data were insufficient for analysis.

After we recorded all the creatinine levels from the period of the ICU stay, we determined the RIFLE category on the first and last days of the ICU stay and on the day that the patient presented the highest category. For those who had more than one creatinine value at admission, the highest level during the first 24 hours was considered. Patients were classified into four categories: Normal renal function (N), Risk (R), Injury (I) and Failure (F); the last three categories defined acute kidney injury. The categories Loss (L) and End-stage Kidney Disease (E) were not considered in the present study.

Renal outcomes were evaluated through the comparison of the last RIFLE category obtained during the ICU stay and the RIFLE score at admission. Depending on renal outcome, patients were classified as favorable (last RIFLE better than that at admission), stable (similar RIFLE categories) and unfavorable (last RIFLE worse than that admission).

The effect of the two strategies was evaluated only in the group of patients that stayed longer than three days in the ICU. Excluded from the study were all patients who had dialytic chronic renal disease and all patients who had less than three values of serum creatinine in a period longer than four days. Excluded patients were considered for intention-to-treat analysis. The study protocol was approved by the Ethics Committee of São Domingos Hospital.

Statistical analysis:

Our primary endpoint was the renal function outcome. Mortality and incidence of newly acquired AKI were secondary endpoints. Data are presented as means $\pm$ standard deviation or medians with interquartile intervals. The chi-square test was used to evaluate the association between categorical variables, and either Student's t-test or the Mann-Whitney U-test was used for evaluation of continuous variables. Multivariate logistic regression analysis was performed to evaluate the impact of age, sex, APACHE (Acute Physiology and Chronic Health Evaluation) III score, diabetes mellitus and hypoglycemia on unfavorable renal outcome, mortality and AKI. The impact of unfavorable renal outcome and AKI on mortality was also analyzed using the same model of logistic regression. All statistical tests were two-sided and were considered to be significant at $p<0.05$. Data were registered in the statistical analysis program SPSS 14.0.

RESULTS

Of the 337 patients included in the original trial, 265 remained in the ICU longer than three days. Among these patients, five were excluded for having chronic renal disease receiving hemodialysis, and 32 were excluded for having less than three measurements of serum creatinine levels during the stay. In total, 228 patients were included in the final analysis.

Demographic data, comorbidities and severity

Among the 228 studied patients, 110 (49%) were in group 1 (IIT) and 118 (51%) in group 2 (CRS). There were no differences between the two groups regarding gender, age,

Table 1 - Main patients' characteristics.

	Group 1 .IIT n = 110	Group 2.CRS n = 118	p Value
Age (y)			
Mean ± SD	58.7 ± 20.4	55.5 ± 21.6	0.25
Female, n (%)	48 (43.6)	59 (50)	0.33
APACHE III score			
Mean ± SD	69.2 ± 22.5	67.1 ± 26.9	0.54
ICU LOS, days			
Median	10	10.5	
Interquartile range	6–22	7–18.5	0.87
Previous diabetes mellitus			
n (%)	39 (35.4)	30 (25.4)	0.11

APACHE: Acute Physiology and Chronic Health Evaluation; ICU: Intensive Care Unit; LOS: length of stay.

previously known diabetes mellitus, APACHE III score and length of stay (LOS) in the ICU (Table 1). The intention-to-treat analysis also showed comparable data between the two groups.

Glycemic control

The median blood glucose levels in the IIT and CRS groups were 132.6 (119.5–150.7) mg/dL and 142 (123.6–171.2) mg/dL, respectively (p = 0.02). The median insulin doses used for glycemic control in groups 1 and 2 were 56.5 (38.8–76.7) IU and 1.3 (0n5.9) IU, respectively (p<0.001). The occurrence of hypoglycemia was higher in the IIT group (20 patients [18.1%]) than in the CRS group (five patients [4.2%]), p = 0.001 (Table 2).

Renal function and mortality

The mean basal creatinine levels calculated for both groups were comparable (Table 3). The RIFLE classification on admission did not show significant differences between the two groups (p = 0.78). We observed that 52.1% of the studied patients presented some level of AKI during their ICU stay, and there was no difference in distribution between the two groups (p = 0.91). AKI was more frequent in diabetic patients (69.5%) than in non-diabetics (43.9%) (p<0.001). Thirty patients needed dialysis: 17 in group 1 and 13 in group 2 (p = 0.56).

Renal outcomes were comparable between the two groups (p = 0.37) (Table 3). In contrast, we observed a significant correlation between the blood glucose levels and the incidence of AKI (p = 0.007) (Table 4).

Of the 228 patients included in the study, 56 (24.5%) died: 24 in group 1 and 32 in group 2 (p = 0.35). Mortality was higher for patients with unfavorable renal outcome (43.2%) compared to those with stable or favorable renal outcome (20.9%) (p = 0.004). Mortality was also higher in patients who presented some level of acute kidney injury (39.2%) compared to those with normal renal function (8.2%) (p<0.001).

In the multivariate logistic regression analysis, only an APACHE III score higher than 60 was identified as an independent risk factor for unfavorable renal outcome. Previous diabetes mellitus and APACHE III scores higher than 60 were risk factors for AKI. Hypoglycemia, APACHE III score>60 and AKI were risk factors for mortality (Table 5).

Table 2 - Insulin therapy and blood glucose levels.

	Group 1.IIT n = 110	Group 2.CRS n = 118	p Value
Blood glucose levels (mg/dl)			
Median	**132.6**	**142**	
Interquartile range	**119.5–150.7**	**123.6–171.2**	**0.02**
Insulin dose (IU/d)			
Median	**56.5**	**1.3**	
Interquartile range	**38.8–76.7**	**0–5.9**	**<0.001**
Hypoglycemia, n (%)	**20 (18.8)**	**5 (4.2)**	**0.001**

Table 3 - Renal outcomes.

	Group 1 Intensive insulin therapy	Group 2 Carbohydrate restrictive strategy	p Value
Basal creatinine (mg/dl)			
Mean ± SD	**0.984 ± 0.146**	**0.980 ± 0.170**	**0.89**
Admission RIFLE			
(n) normal	**70**	**78**	
Risk	15	18	0.78
Injury	11	8	
Failure	10	12	
Acute kidney injury n (%)	**57 (51.8)**	**62 (52.5)**	**0.91**
Renal function outcome			
Unfavorable	17	20	
Stable	64	76	0.37
Favorable	29	22	

DISCUSSION

Our comparison of two strategies of glycemic control in a mixed population of critically ill patients did not show a significant difference in the incidence and severity of acute kidney injury evaluated using RIFLE criteria. However, we observed that an increase in blood glucose levels beyond normal values was associated with increased incidence of AKI.

In a previous study in which we compared the safety and efficacy of intensive insulin therapy with a carbohydrate-restrictive strategy, we used the need for dialysis as the criterion to define renal dysfunction, and no difference was observed between the two groups. The present study used a more accurate and sensitive tool, the RIFLE criteria, that includes a wide spectrum of renal dysfunction and not merely the more severe forms of the disease.

Although Van den Berghe et al.[1] showed a significant reduction in the incidence of acute renal failure in patients submitted to intensive insulin therapy, these authors used

Table 4 - Acute kidney injury according to glycemic levels.

Glycemia	Normal	Kidney Injury	Total
< 120	33 (60,0)	22 (40,0)	55 (24,1)
120 a 150	49 (51,6)	46 (48,4)	95 (41,7)
150 a 180	19 (43,2)	25 (56,8)	44 (19,3)
> 180	8 (23,5)	26 (76,5)	34 (14,9)
Total	109 (47,8)	119 (52,2)	228

p = 0.007

Table 5 - Multivariate logistic regression.

	Renal outcome		AKI		Mortality	
Variable	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)
Age	0.42	NS	0.90	NS	0.20	NS
Gender	0.07	NS	0.70	NS	0.09	NS
APACHE III	0.02	2.92 (1.17–7.29)	<0.001	4.93 (2.63–9.27)	0.02	0.36 (0.15–0.90)
Diabetes	0. 06	NS	<0.001	3.47 (1.72–7.01)	0.51	NS
Hypoglycemia	0.30	NS	0.11	NS	< 0.003	0.20 (0.07–0.59)
AKI	-	-	-	-	< 0.001	0.20 (0.08–0.49)
Renal outcome	-	-	-	-	0.30	NS

the need for dialysis as the criterion to define acute renal failure. This restricts the analysis to patients with severe renal dysfunction.

The lack of consensus regarding the definition of acute renal failure that lasted until recently created difficulties in evaluating the effects of different therapeutic interventions on the incidence and severity of acute kidney injury. The publication of the RIFLE criteria in 2004[5] that standardized the definition of AKI was followed by studies with large patient populations that validated those criteria, creating a tool that unified the diagnosis of AKI. RIFLE allowed the analysis of AKI's full spectrum of severity and not just the most severe forms of the disease.

Lecomte et al.[14] were the first to use the RIFLE criteria to compare AKI incidence in patients who had been submitted to two different strategies of glycemic control. This study showed that, in non-diabetic patients undergoing cardiac surgery, strict glycemic control during and after surgery was associated with a significant decrease in AKI and mortality, with a minimal incidence of hypoglycemia (0.17%). Rather than analyzing patients in the perioperative period, our study included only patients that remained in the ICU for at least three days. We based our strategic focus on that of the Van den Berghe et al. study,[2] which affirmed that intensive insulin therapy requires a minimal period of time to have an effect and that more benefits are observed after three days of intervention.

Recently, the Acute Kidney Injury Network (AKIN)[15] proposed a modification of the RIFLE criteria with the objective of increasing its sensitivity. Studies that have compared the two sets of criteria have shown little difference between them.[16,17]

In this study, the carbohydrate-restrictive strategy was comparable to intensive insulin therapy in terms of effects on the incidence of AKI. However, the CRS group had a significantly lower incidence of hypoglycemia. It is well documented that hypoglycemia is associated with higher mortality and neurologic dysfunction. In the Van den Berghe study[2], the logistic regression analysis identified hypoglycemia as an independent risk factor for death. The multicenter GLUCONTROL[18] study was interrupted prematurely because of this kind of risk. The interruption was required because of the high incidence of hypoglycemia and the significantly higher mortality in patients that presented with this complication. In the present study, multivariate regression analysis showed that hypoglycemia was a risk factor for death.

The incidence of AKI in the patients in our sample was high (52%) when compared to that observed by Ostermann et al.[7] (38.5%), who also observed patients in an ICU. Uchino et al.[6] observed a smaller incidence of AKI (18%) when they analyzed all the patients admitted to a tertiary university hospital. Like our own study, both of these studies showed a significant impact of AKI (as defined by the RIFLE criteria) on mortality. The multivariate logistic regression analysis of our study reinforced that AKI is an independent risk factor for death.

This study has some limitations. It is a retrospective analysis of patients that were included in a prospective randomized trial. Some patients were excluded from the analysis because they had less than three creatinine determinations during their ICU stay. It is also worth noting that because rigorous measurements of urine output were not required in the original trial, RIFLE classification was based only on serum creatinine levels. It is not possible to state whether the measurement of urine output would have changed the results of this study. Some studies suggest that patients who had a RIFLE classification based on creatinine values were more severely ill than patients in the same risk category whose classification was defined by urine volume alone.[19] The studies by Uchino et al.[7] and Ostermann et al.[8] also defined RIFLE category based only on serum creatinine.

CONCLUSION

Intensive insulin therapy and a carbohydrate-restrictive strategy were comparable in their effects on the incidence of acute kidney injury evaluated using the RIFLE criteria. However, we observed that an increase in the blood glucose levels beyond normal values was associated with an increase in the incidence of AKI. This finding, as well as the higher incidence of hypoglycemia, suggests that a carbohydrate-restrictive strategy is safer than and as efficient as intensive insulin therapy in preventing acute kidney injury in critically ill patients.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors participated in this study, read the manuscript and attest to the validity and legitimacy of the data and its interpretation.

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